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A Discussion of Exposure Science in the 21st Century: A Vision and a Strategy

Paul J. Lioy^{1,2}, Kirk R. Smith^{1,3}

¹NRC Expert Committee on Exposure Science in the 21st Century

²Environmental and Occupational Health Sciences Institute, UMDNJ - Robert Wood Johnson Medical School and Rutgers University, Piscataway, New Jersey, USA

³School of Public Health, University of California, Berkeley, Berkeley, California, USA

Corresponding Author:

Paul J. Lioy, 170 Frelinghuysen Road, Piscataway, NJ 08854, 848-445-0155,
plioy@eohsi.rutgers.edu

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Abbreviations: NIEHS – National Institute of Environmental Health Sciences; NRC – National Research Council; USEPA – United States Environmental Protection Agency

Abstract

Background: The National Research Council (NRC) of the National Academy of Sciences recently published the report: *Exposure Science in the 21st Century: A Vision and a Strategy*. The expert Committee undertaking this report included expertise from ecology, chemistry, exposure science, toxicology, public health, bioethics, engineering, medicine, and policy.

Objectives: Although commissioned by the USEPA and the NIEHS, the report is solely the consensus product of the independent volunteer committee, whose findings were subject to the rigorous peer-review procedures of the NRC. In addition to reviewing the history and current status of exposure science, the report lays out a vision for the future and makes recommendations which include both short-term and long-term milestones.

Discussion: This Commentary is written for members of the scientific community in fields that are aligned with environmental and public health to help them appreciate the full breadth of the vision, and to understand the framework developed in order to move the vision forward.

Conclusion: Important excerpts as well as paraphrased statements from the report appear in this commentary; however the general observations and comments are our own.

Introduction

The concept of exposure for non-occupational settings outside of ionizing radiation was first introduced in the early 1980s and mentioned in *Risk Assessment in the Federal Government: Managing the Process* (NRC 1983), also known as the “Red Book.” It described exposure assessment as an analysis tool that was limited to evaluating single media problems.

Subsequently, after a series of successes in the characterization of population exposures, a scientific field emerged, exposure science, using as its foundation field studies, laboratory experiments, and the development of fundamental equations (Lioy 1990; Ott 1995; Smith 1988a, b; USEPA 2009; Wallace 1987). The first NRC committee on exposure published *Human Exposure Assessment for Airborne Pollutants: Advances and Opportunities*, also called the “White Book” (NRC 1991) which, along with the start of a scientific society and federal funding for various programs, provided a path forward for the field that lasted into the 21st Century. The field, now known as “Exposure Science,” continued to evolve with the founding in 1989 of the International Society for Exposure Assessment and the associated *Journal of Exposure Assessment and Environmental Epidemiology*. The Society and the journal were later renamed International Society for Exposure Science and *Journal of Exposure Science and Environmental Epidemiology* and this was also formally acknowledged by the journal *Environmental Health Perspectives* in the 2008 editorial “Time for a change: from exposure assessment to exposure science” (Lioy 2008).

Over the past few years it became clear, however, that because of expanded expectations for use of exposure assessments along with the emergence of new technologies for exposure measurements, e.g. high throughput genomic tools, personal monitors, and source-to-dose modeling systems, that the status of the field in the 21st century needed to be reexamined.

Guidance was needed to achieve sustainable growth in both occupational and human exposure research toward the goal of improving public health. Thus, the new NRC committee was constituted to provide recommendations on research activities that could assist in providing a basis for: (1) better coordination with other fields in the environmental health sciences and ecology; (2) better approaches to address scientific, regulatory and societal challenges; (3) new approaches to provide exposure information for large segments of the population; and (4) embrace approaches for better human and ecosystem protection. With this in mind the USEPA and the NIEHS funded a new NRC study. The Committee (see report for membership) recently completed its analyses and published the “Gold Book” - *Exposure Science in the 21st Century: A Vision and a Strategy* (NRC 2012).

The overall charge was the following:

“A National Research Council committee will develop a long-range vision for exposure science and a strategy with goals and objectives for implementing the vision over the next 20 years, including a unifying conceptual framework for advancement of exposure science to study and assess human and ecologic contact with chemical, biologic, and physical stressors in their environments. In developing the vision and the strategy, the committee will consider exposure-assessment guidelines and practices used by the Environmental Protection Agency and other federal agencies, the use and development of advanced knowledge and analytic tools, and ways of incorporating more complete understanding of exposure into risk assessment, risk management, and other applications for the human health and ecologic services. The study will focus on the continuum of sources of stressors, their fate in our changes in the environment, human and ecologic

exposure, and resulting doses or other relevant metrics that are relevant to outcomes of concern” (NRC 2012).

The report was envisaged to potentially be a companion to two other recent NRC reports, “Toxicity Testing in the 21st Century: A Vision and a Strategy” (NRC 2007), and “Science and Decisions: Advancing Risk Assessment” (NRC 2009). Notably, however, the charge was set much more broadly than for these other two reports, i.e., to explore the entirety of exposure science including its application in ecology, not just assessment or testing.

Exposure Science for the 21st Century

Defining the Field

There are a wide array of problems that require exposure science, since humans (and other species) can come into contact with physical, chemical, and biological agents every day and during natural and other catastrophic events. Consequently, the report dealt with major issues in exposure science, but it could not cover all topics. To meet its charge, the Committee decided to use a focused definition of exposure science NRC (2012):

“Exposure science is defined by this committee as the collection and analysis of quantitative and qualitative information needed to understand the nature of contact between receptors (such as people or ecosystems) and physical, chemical, or biologic stressors. Exposure science strives to create a narrative that captures the spatial and temporal dimensions of exposure events with respect to acute and long-term effects on human populations and ecosystems.”

This is not significantly different from the definition by Barr (2006), which has been adopted by the field of human exposure science: “Human Exposure Science studies human contact with chemical, physical or biological agents occurring in their environments, and advances knowledge of the mechanisms and dynamics of events either causing or preventing adverse health outcomes.” The Barr definition emphasizes dynamics and mechanisms of contact, not just measurements. In addition, the definition can easily be amended to encompass ecological exposures. Based upon the charge, the Committee limited its analysis to the contact with chemical, physical and biological stressors, and did not specifically focus on lifestyle, social conditions, and behavior, except as affecting the way those stressors come into contact with people or ecosystems (See Figure 1). The report notes, however, that lifestyle, social conditions, and behavior can be considered stressors in themselves and these relationships are active areas of research. We believe that these aspects of exposure science should be considered in future evaluations of exposure science applications to epidemiology, risk assessment, risk management and regulations.

From the source to the exposure to the dose

The basic concept behind exposure science is that the point of contact between the organism at risk and the environment through which the stressor operates is the optimal point for both understanding and controlling the effect of stressors on human and ecosystem health. It links directly to the sources that might be controlled and to the internal environment of the organisms that are of concern.

This point is illustrated in Figure 1. The content of exposure science includes the core elements of the field, and provides a conceptual framework that identifies and links sources of stressors,

environmental intensity, time-activity and behavior contact of stressors and receptors and outcome contact. It is modified from the classic source-to-dose continuum that shows a linear relationship from source to effect (e.g. Liroy 1990; Smith 1988a). The revised framework has a number of important modifications:

1. The feedback loop shows the possibility that an outcome experienced by an individual or population can be spread to others. Thus, exposure science addresses the factors that lead to both the initial exposures to stressors as well as the spread of stressors from affected populations to another population or individuals. Some examples include diarrhea-causing organisms spread from infected humans back into the environment and then leading to contact by and disease outbreaks in other humans, and sarin gas re-emitted from the lungs of terrorist victims and causing exposures among emergency room health care workers.
2. The feedback loop includes how health outcomes among people or ecosystems can alter activities and behaviors among individuals and subpopulations affecting subsequent exposure. Thus, the health effects can change exposures, as well as vice versa. Asthmatics, for example, may change their behavior and activities that affect their exposures.
3. The separation of time-activity into its own category emphasizes its importance in exposure science.
4. The explicit inclusion of “upstream” forcers of exposure shows more clearly that they are integral to the field; for example, in looking at the implications of energy, land use, or transportation policies for exposures.

5. The explicit recognition that at the receptor the role of internal marker measurements is part of exposure science.

Even with the added value of each of these 5 points, the point of contact between stressors and human and other receptors remains the central concept, and goal of effective implementation of the scientific principles of the field.

Figure 1 provides an update to the classic framework that, if used effectively, can provide opportunities for expansion of the science to deal with a broader range of critical public and environmental health issues.

A major concept discussed throughout the report is that of internal exposure. As previously mentioned by Cohen Hubal et al. (2010), new technology can ensure that exposure science includes both external and internal markers, as appropriate. We believe this would improve links with other fields in the environmental health sciences, e.g. toxicology and epidemiology, with applications to risk assessment. The report notes that over the past 15 years there is a “greater emphasis on the use of internal markers of exposure to assist in defining exposure-response relationships.” The Committee identified measurements of chemicals and metabolites in the body, oxidative modifications of DNA, and metabolomics coupled with pharmacokinetics as basic examples of internal markers of exposure. As the Committee noted, the linkage of exposure science results for internal, as well as external, markers of exposure, are also needed to inform the selection of relevant concentrations of stressors and chemicals for high throughput toxicity testing.

Figure 2 illustrates the relationship among sources, outcomes, and the dynamics of exposure. In addition, it places internal exposure between external exposure and the dose delivered to a target

site. So, one person's concern for the measurement or estimate of internal exposure can be another person's indicator of an internal dose (Lioy 1990). More importantly, the expansion of exposure science to include internal markers of exposure can provide opportunities for dialog among scientists from the different disciplines in the environmental health sciences. This will increase the probability of reacting more quickly to assist a diseased population to provide treatment, but to also use "smart" science to reduce or mitigate exposure in all parts of the world. What is also critical to note in Figure 2 is the acknowledgement that source to outcome analyses are bi-directional processes which is illustrated by a toxicant flowing to the point of yielding an outcome, and then information on exposure outcomes being used to identify approaches to intervention and prevention of disease by source control or replacement, a point also noted in the report. This will lead to the development of better policies for toxicants that are already used in commerce and industrial processes.

The Eco-Exposome

The Committee introduced a new concept - the "eco-exposome" - to encapsulate the vision for advancing exposure science in the 21st century. It is defined as the extension of exposure science "from the point of contact between a stressor and receptor inward into the organism and outward to the general environment including the ecosphere;" thus, embracing the use of both internal and external markers of exposure. The definition addresses the confusion that was beginning to evolve since the original exposome concept seemed to promote measurements that were primarily inward, i.e. internal markers of exposure (Wild 2005, 2012). Lioy and Rappaport (2011) discussed the need to link internal and external markers of human exposure as part of the exposome, and these thoughts were also reflected in Wild (2012). The eco-exposome concept also captures the important link outward from the organism (i.e. human or other species) to

single or multi pollutant sources, which is critical in making effective control decisions. As the Committee states throughout the report, the eco-exposome narrative will “improve [the collection of] exposure information for making informed decisions on human and ecosystem health protection.” We are, however, anticipating a significant dialog on this issue since; as with the exposome, it is a proposed concept.

The report discusses many new measurement and detection tools and mathematical modeling systems, and that the eco-exposome opens new paths to encourage the continued development of innovative tools to address the spectrum of scientific questions facing many segments of public and environmental health.

Achieving the Exposure Science Vision

The four major activities and research points identified by the Committee to achieve its vision of the extension of exposure science from the point of contact between stressor and receptor inward into the organism and outward to the general environment, including the ecosphere are:

“Assess and mitigate exposures quickly in the face of emerging environmental-health threats and natural and human-caused disasters. For example, this requires expanding techniques for rapid measurement of single and multiple stressors on diverse geographic, temporal, and biologic scales. That includes developing more portable instruments and new techniques in biologic and environmental monitoring to enable faster identification of chemical, biologic, and physical stressors affecting humans or ecosystems.

Predict and anticipate human and ecologic exposures related to existing and emerging threats. Development of models or modeling systems will enable us to anticipate and characterize exposures that had not been previously considered. For example, predictive

tools will enable development of exposure information on thousands of chemicals that are now in widespread use and enable informed safety assessments of existing and new applications for them. In addition, strategic use of such diverse information as structural properties of chemicals, non-targeted environmental surveillance, biomonitoring, and modeling tools, are needed for identification and quantification of relevant exposures that may pose a threat to ecosystems or human health.

Customize solutions that are scaled to identify problems. As stated in *Science and Decisions: Advancing Risk Assessment* (NRC 2009), the first step in a risk assessment should involve defining the scope of the assessment in the context of the decision that needs to be made. Adaptive exposure assessments could facilitate that approach by tailoring the level of detail to the problem that needs to be addressed. Such an assessment may take various forms, including very narrowly focused studies, assessments that evaluate exposures to multiple stressors to facilitate cumulative risk assessment, or assessments that focus on vulnerable or susceptible populations.

Engage stakeholders associated with the development, review, and use of exposure-science information, including regulatory and health agencies and groups that might be disproportionately affected by exposures—that is, engage broader audiences in ways that contribute to problem formulation, monitoring and data collection, access to data, and development of decision-making tools. Ultimately, the scientific results derived from the research will empower individuals, communities, and agencies to prevent and reduce exposures and to address environmental disparities.”

These key aspects of the vision provide a firm foundation for filling the boxes and flow of information associated with Figure 1, and also indicates that during the completion of the

research and other scientific activities it is necessary to provide access to data by various stakeholders to eventually mitigate or prevent future exposures. Finally, it brings in to focus the need to be prepared to quickly evaluate and mitigate population and occupational multi-pollutant or single pollutant exposures during disasters including terrorist attacks or military actions.

More practically, although not delving into the available measurement methods, the report supports moving away from dependence on default “exposure factors” for preparing risk and environmental impact assessments and increasing expectations for actual measurement of important variables, and then using these measurements to model exposure for specific situations. The report continues to support the concept of the “exposure pyramid” used in epidemiologic and risk assessment studies, in which even simple metrics, such as percent of households exposed, can sometimes be a useful cost-effective exposure measure. At the same time, investigators should consider the trade-offs in going to more costly and intrusive measurement platforms, such as personal and biomonitoring, in terms of reduction of exposure misclassification and improving intervention and prevention strategies (NRC 1991).

The goal for achieving the vision should be to design and develop programs that include the smart science approaches associated in the above to provide information and analyses that can be applied to solve current and unanticipated problems, e.g. natural events and terrorist attacks. Further, data acquisition must be coupled with significant opportunities to assemble and interpret data (Lioy 2010).

Informatics is discussed in the report as an important tool for assembling data from the results obtained from the collection of internal (biomonitoring) and external (personal and microenvironmental monitoring) from, for example, high throughput instrumental analyses and

continuous or smart phone based technology, respectively. However, the ability to use and interpret such data is still in its infancy. To address this issue the Committee has strongly acknowledged that implementation of its vision will “depend on the development and cultivation of scientists, engineers, and technical experts in multiple fields to educate the next generation of exposure scientists...” In the United States this will require “an increase in the number of academic pre-doctoral and post-doctoral programs” and provide “short term certification programs” to meet immediate needs. In the era of reduced funding the Committee does indicate that agencies must start to have trans-agency coordination and resources for all aspects of exposure science research and education. Clearly, such programs can lay a foundation for the development of similar activities on the international landscape; both in developed and underdeveloped countries.

The report provides examples of demands for research that can be conducted by exposure science, and these are summarized in Figure 3. There are societal, market, health and environmental, and policy/regulation demands. Of the four, the most well-known are the health and environmental demands, but the others are critical in a national perspective and, during the realization of the vision, international perspectives. Market demands will include control or replacement of materials in consumer products, before sale as well as after sale and use. Societal demands will include aspirations from individuals and communities to understand and participate in the reduction of single or multi-route exposures and consequential environmental health risks. However, it should be noted that the demands transcend geopolitical boundaries. Thus, they can be drivers for addressing both domestic and global problems [e.g. energy and fuels (Smith 1988b; Smith 1993; Smith et al. 2012)].

The overall scope of the report's recommendations for expanding the research activities and types of data required for the field are summarized in Figure 4, which illustrates how some of the new tools described in detail within the report (e.g. Chapter 5) can be placed within the framework to improve the collection of new exposure data and models to improve linkages to outcome assessment. The types of tools mentioned in Figure 4 are examples evaluated for inclusion in the report and, depending upon the route of exposure and the agents of concern, the needs for tools associated with the boxes may change (NRC 2012). As trans-agency opportunities are discussed in the US and considered by other agencies around the globe, augmented versions of the graphic would be useful to identify critical needs and paths forward in exposure science for environmental and ecological health, emergency response, risk assessment and risk management.

Final Thoughts

Although broadly framed to include ecological and human impacts, the report's charge was to focus on issues of particular concern to the United States and thus it does not directly address, for example, the many special exposure issues of developing countries, where environmental health threats are the greatest at all scales: from household to community to global issues (Lim et al. 2012; Smith and Ezzati 2005) . This could well be the grist of a future report.

In addition, given the report's charge, it does not address the past and potential use of regulation and management of exposures from either single or multiple routes of contact in both environmental and occupational settings. More sophisticated use of exposure science represents potential opportunities for protecting more workers and members of the public at less expense

than current practices, through what could be called smart regulation and management that also maintains the highest standards of equity. This would be an excellent subject for a future report.

With its mandate to focus on the future, the report also does not explore the still considerable improvements in current and past epidemiologic and risk studies that are promised by more complete application of some of the classic concepts of exposure science, such as “total exposure,” – capturing all routes, places, times and durations of exposure. An example is the growing evidence of apparently non-threshold and sometimes even supralinear effects at what were once considered low exposure levels: the lower the level of detected exposure; however, the higher the potential for exposure misclassification due to multiple pathways and routes of contact. This also would be a timely subject for assessment.

Finally, the vision presented in the report to mitigate and/or prevent future impacts of chemical, physical and biological stressors is both bold and achievable. However, it requires resources to complete the investigations required to develop and use external and internal analyses of exposure and build databases associated with exposures to individuals and large populations. Only then, can source to effect modeling systems simulate the dynamics and mechanisms of contact with chemical, physical and biological stressors. The results can be used to mitigate exposures to such stressors associated with single or multiple routes of contact. Concurrently, the next generation of exposure scientists need to be trained to implement the vision, and embrace and quantitatively elaborate on the concept of the eco-exposome. Such an approach can be used to examine and solve human and environmental health problems around the world.

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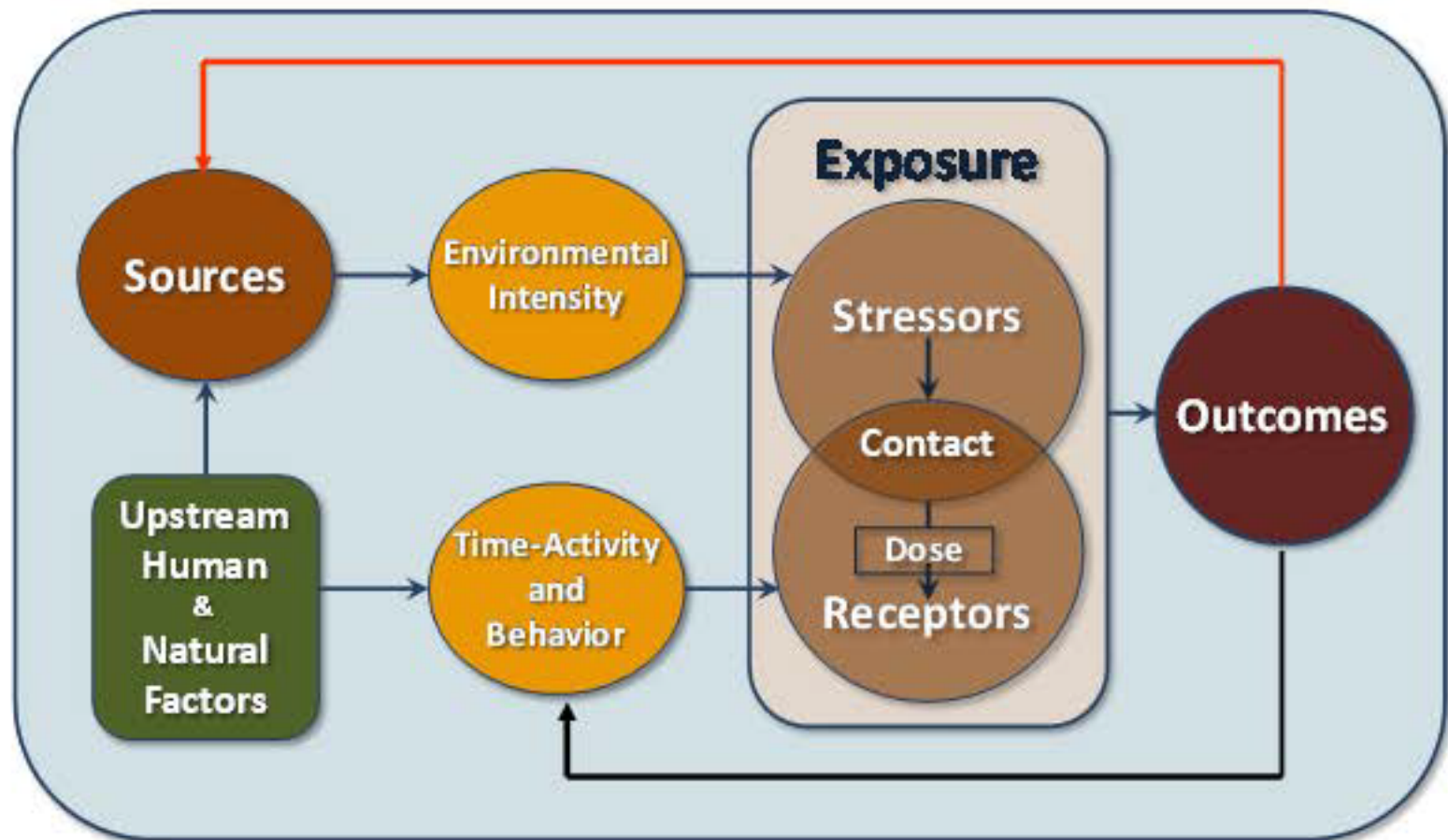
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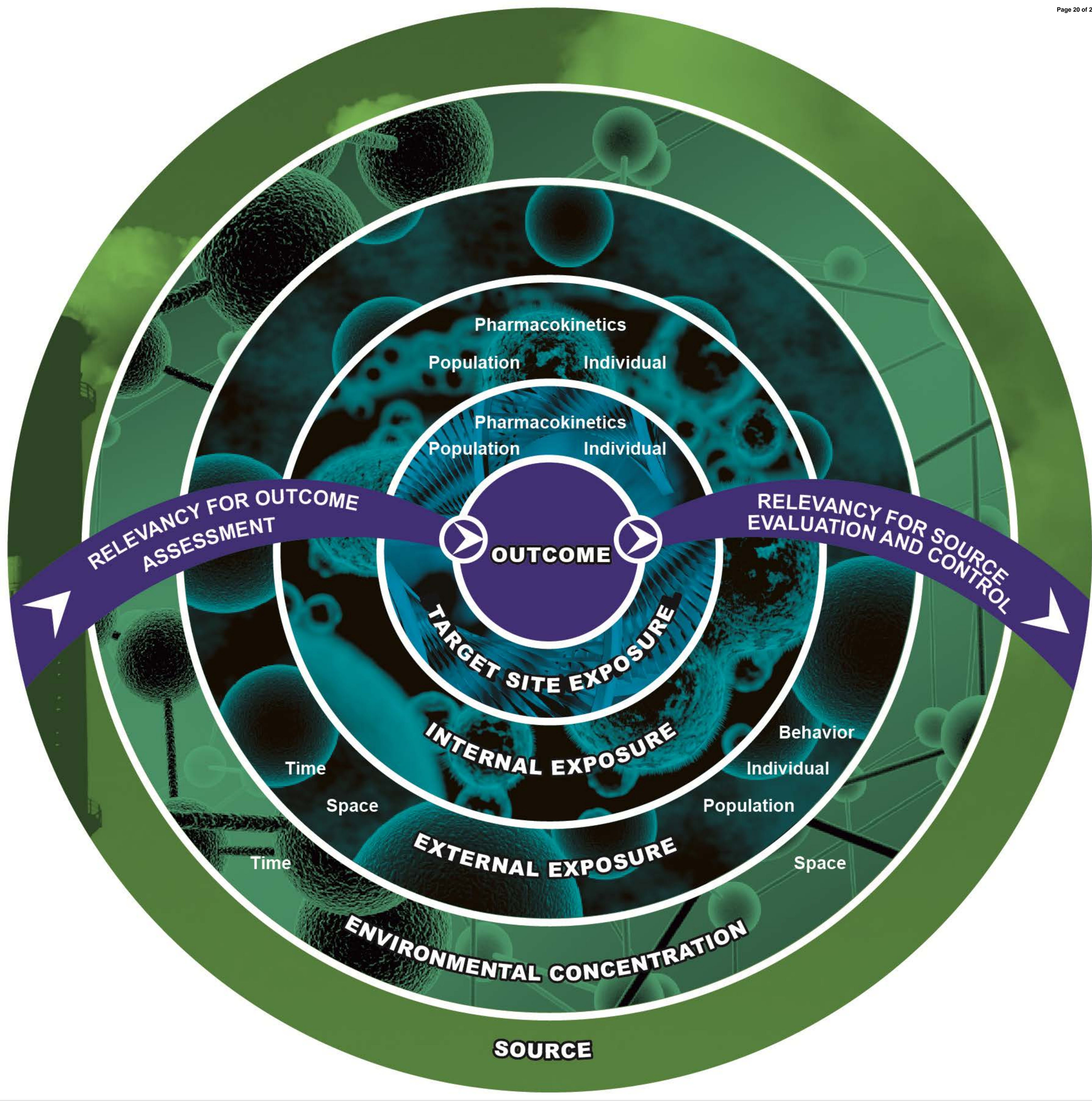
Figure 1. Conceptual framework showing the core elements of Exposure Science as related to both humans and ecosystems [From NRC (2012); reproduced with permission, all rights reserved]

Figure 2. A bidirectional view of the source to effects continuum [From NRC (2012); reproduced with permission, all rights reserved]

Figure 3. The four major demands for exposure science [From NRC (2012); reproduced with permission, all rights reserved]

Figure 4. Selected scientific and technological advances for measuring and monitoring considered in relation to the conceptual framework in Figure 1 [From NRC (2012); reproduced with permission, all rights reserved]





Societal Demands

Page 21 of 22

Exposure Science

Policy/Regulatory
Demands

Market
Demands

Health and
Environmental
Science
Demands

